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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,045	BOUSTANY ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/23/02;5/20/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *11-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *502* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed January 23, 2002. Currently, claims 1-46 are pending. Claims 11-46 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-10, drawn to a method of screening a subject for a proliferative disease risk factor by detecting upregulation of the CLN3 gene.

Group II, claim(s) 11-16, drawn to a method of screening a compound for efficacy in the treatment of a proliferative disease.

Group III, claim(s) 17-24, drawn to an in vitro method for screening compound.

Group IV, claim(s) 25-32, drawn to a method of inhibiting the growth of proliferative cells by administering a vector expressing a heterologous nucleic acid which encodes a product that inhibits the expression of the CLN3 gene.

Group V, claim(s) 33-40, drawn to a recombinant vector containing and expressing a nucleic acid which encodes a product that inhibits the expression of the CLN3 gene.

Group VI, claim(s) 41-46, drawn to a method of screening compounds for efficacy in treating a proliferative disease by determining whether compounds bind to CLN3 gene products.

3. The inventions listed as Groups I-VI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons.

A 371 case is considered to have unity of invention only when there is a technical relationship among those inventions involving one or more of the same or corresponding technical features. The expression "special technical feature" means those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art. While the instant claims all involve the CLN3 gene, it is clear from the art that said CLN3 gene does not define a contribution over the prior art. The special technical feature, which defines a contribution over the art appears to be the presence of upregulation of the CLN3 gene in a subject as indicative of increased risk of developing a proliferative disorder. All of the groups do not appear to have this same special technical feature. For example, Group II is directed to a method of screening for compounds for efficacy in the treatment of a proliferative disorder by obtaining a group of patients, administering a compound and determining the efficacy of the compound in treatment. Moreover, Group III requires the inhibition of the CLN3 gene; Group IV requires administering a vector which expresses a heterologous nucleic acid which encodes a product that inhibits the expression of the CLN3 gene; Group V is directed to a vector; and Group VI is directed to screening for compounds which bind to CLN3 gene products. Therefore, the Groups do not appear to share the same special technical feature which defines a contribution over the art.

Moreover, as provided in MPEP 1850, states that "the method for determining unity of invention under PCT Rule 13 shall be construed as permitting, in particular, the inclusion of any one of the following combinations of claims of different categories in the same international application." The instant claims do not appear to fall within any one

of these categories set forth for unity of invention. Therefore, the claims may be properly restricted.

4. During a telephone conversation with Ken Sibley on May 23, 2003 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-10. Affirmation of this election must be made by applicant in replying to this Office action. Claims 11-46 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

6. This application is a 371 of PCT/US99/24695, filed October 21, 1999 which claims priority to provisional application 60/105,262, filed October 22, 1998.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

Drawings

7. The drawings are acceptable.

Sequence Rules

8. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

For example, on pages 17-18 and 27 of the instant specification, sequences have not been identified by SEQ ID NO:. Appropriate correction is required.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-10 are broadly drawn to methods of screening a subject for a proliferative disease risk factor, by detecting the presence or absence of upregulation of the CLN3 gene wherein the upregulation of the CLN3 gene in the subject is indicative of an increased risk of developing a proliferative disease. The claims broadly encompass screening any subject, including, but not limited to humans, dogs, cats, horses. Moreover, the claims are broadly drawn to any proliferative disorder which is defined in the specification to encompass any cancer, arthritis, asthma, fibrosis, for example.

The teachings of the specification and working examples

The specification teaches an analysis of breast cancer cell lines, colon cancer cell lines (Figure 9-12, page 7-8), melanoma cell lines, neuroblastoma cell line, glioma cell line and glioblastoma cell line. The specification teaches that the melaonma cell lines actually had "less CLN3 expressed" (page 8, lines 15-18). Each of these analyses was performed on cell lines. The specification fails to provide any evidence that a similar pattern of over-expression is present in actual tumor tissue. There is no evidence that the correlation between upregulation of CLN3 would be present in actual tissues. Moreover, in the analysis provided, not all of the cell lines were correlated in the same manner with CLN3 expression. The over-expression of CLN3 in cancer cell lines is not sufficient evidence to enable one skilled in the art to determine that this nucleic acid would necessarily be over-expressed in primary tumor tissue as compared to non-tumor tissue.

The specification teaches that the term "proliferative disease" as used herein "refers to both cancer and non-cancer disease. The specification teaches that "illustrative non-cancer diseases include inflammatory and/or immunoproliferative disorders such as arthritis, fibrosis, asthma and allergies" (page 9, lines 26-30). Moreover, the specification teaches that cancers may include leukemia, soft tissue and bone sarcomas, neuroendrocrine tumors, squamous carcinomas and adenocarcinomas (page 10, lines 1-10).

Moreover, the instant specification contemplates the use of the invention on animal subjects such as cats, dogs, and horses for veterinary purposes (page 10, lines 5-10). The instant specification fails to provide any analysis of the CLN3 genes for each of these species. Furthermore, the instant specification has not taught the CLN3 gene sequence for equine (horses). The skilled artisan would be required to obtain the CLN3 gene from the additional species prior to performing the screening method and determine whether an association exists.

The specification has no working examples of solid tumors in a representative number of proliferative disorders, as defined by the instant specification. While there are cell line examples for human cancers, there are no tissue working examples for allergies, fibrosis, arthritis and asthma in various species including dog, cat and horse.

The unpredictability of the art and the state of the prior art

There is a great deal of unpredictability in the expression of nucleic acids as indicative of diseases. As noted by the instant specification, not every cell line acts in a concordant manner, see the melanoma cell line, for example.

Moreover, Dermer *et al.* (Biotechnology Vol. 12, March 1994, p. 320) teach that cell lines are a poor representation of malignancy because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its

artificial environment. Dermer *et al.* state that "the petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease."

With regard to a specific nucleic acid, namely PARP, Chabert *et al.* (Int. J. Cancer: 53, 837-842 (1993)) compare PARP gene expression, enzymatic activity and quantities in 3 animal tumor cell lines in culture verses those transplanted into a compatible host, an found that, for "a given tumor cell line, marked differences exist in poly(ADPR)P gene expression and enzymatic activity between cultured cells and cells obtained from solid or ascitic tumors. Indeed, poly(ADPR)P gene expression, endogenous activity and amount are higher in exponentially growing cells than in *in vivo* tumors (p. 837, see also Fig. 1)." Chabert *et al.* further suggest that such discrepancies in enzymatic activity between cell culture and in vivo growth conditions exist because of differences in proliferation rates and/or environmental conditions (p. 841). Thus, before determining that a certain cell line is associated with a proliferative disease, the skilled artisan would be required to perform experiments to ensure there is a correlation.

The post filing date art further confirms the unpredictability of this area. Rylova et al. (Cancer Research, Vol. 62, pages 801-808, February 1, 2002) teaches that CLN3 mRNA is not overexpressed in either melanoma or pancreas cell lines (see Figure 1, page 803).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this association to solid tumors from individuals rather than cell lines and to any proliferative disease.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Guidance in the Specification.

The teachings of the specification do not establish that one could actually detect upregulation or overexpression of CLN3 as an indicator of proliferative diseases in general, let alone in any proliferative disorder including arthritis, asthma or fibrosis in any species including but not limited to dogs, cat and horses. Rather the teachings of the specification asserts that CLN3 is expressed at higher levels in several cell lines, but not differentially expressed in other cell lines. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. While one could conduct additional experimentation to determine whether, e.g., expression of CLN3 might be associated with e.g., certain types of proliferative disease, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue.

The specification merely discloses upregulation of CLN3 in a few cell lines, not all cell lines, which are asserted to be cancer models. While the ordinary practitioner in this field is highly skilled, the evidence presented in the specification does not provide even a highly skilled practitioner means to overcome the limitations of evidence derived from cell lines and to make and/or use CLN3 as a method for cancer diagnosis and/or detection with any reliability. As discussed by Dermer *et al.* and Chabert *et al.* the level of predictability between the activity of tumor cell lines and actual tumor tissue is very low, and thus practicing this invention would require unreasonable experimentation on the part of the practitioner to further screen actual tumor tissue to test for a connection between CLN3 over-expression and cancer.

However, as noted above, cell lines are not sufficient models for cancer. In the absence of guidance from the specification, one skill in the art may look to the teachings of the prior art for enablement of the claimed invention. However, the closest prior art does not provide support for the use of CLN3 expression as an indicator for all proliferative diseases, including cancers, asthma, arthritis, fibrosis etc. Thus, it is unpredictable as to whether one could successfully use the claimed invention, and given the fact that neither the specification nor the prior art provide evidence of a correlation or association between CLN3 expression and proliferative disease, it is further unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention. Accordingly, it would require undue experimentation for a skilled artisan to use the claimed invention. In light of the teachings in the prior art, and the general unpredictability concerning the activity of CLN3 in tumor cell lines versus actual tumor tissue, the specification does not enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the presence of a possible association between CLN3 in cancerous cell lines for humans, the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the cell lines. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define an association for screening a subject, the lack of guidance provided in the specification, and the absence of a working examples directed at subjects balanced only against the high skill level in the art, it is the position of the

examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-10 are indefinite over recitation of Claim 1 because it is unclear as to whether the claims are intended to be limited to methods of screening a subject for a proliferative disease risk factor or indicating that a subject is at increased risk of developing a proliferative disease. The claims are drawn to a method of screening a subject for a proliferative disease risk factor, however the final step is one of indicating a subject is at increased risk for developing a proliferative disease. Accordingly it us unclear whether the claim is one for screening a subject for a risk factor or whether the claims are intended to be directed to a method of screening a subject for an increased risk of developing proliferative disease.

B) Claim 10 is indefinite over the recitation "said patient" because "said patient" lacks proper antecedent basis. Claim 1 is directed to a subject, rather than a patient. The rejection may be easily overcome by amending the claim to recite "said subject."

Conclusion

11. No claims allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 6:00 a.m. to 3:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
Patent Examiner
September 5, 2003